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On the safety of intravenous iron, evidence trumps conjecture

Anemia is one of the world's most common disorders. In 2010, global anemia prevalence was 32.9%, affecting over 2.2 billion people, and iron deficiency the most common of the causes.¹ Oral iron, while inexpensive and effective when taken and tolerated, is frequently associated with unpleasant gastrointestinal side-effects, resulting in high rates of non-adherence. Furthermore, in conditions such as inflammatory bowel disease, end-stage renal disease, heavy uterine bleeding, hereditary hemorrhagic telangiectasia, and following major and bariatric surgery, oral iron may be ineffective due to its inability to keep up with losses or may be harmful by worsening the underlying pathology or by causing significant gastrointestinal side-effects. Under these circumstances, intravenous iron administration is the repletion route of choice. Currently, five formulations are available in the United States and six in Europe. Based on the overwhelming amount of published evidence, intravenous iron is nearly universally effective, with serious adverse events being very rare, estimated to be less than 1:200,000 administrations.² Nonetheless, there is an ongoing prejudice against the use of parenteral iron largely based on experience with earlier preparations that are no longer available and which were associated with unacceptably high rates of anaphylactic reactions. Adding to these concerns is the use of spontaneous reporting of serious adverse events, a proscribed method of determining relative safety profiles of different formulations,³ and corroborated by a recent guidance document by the European Medicines Agency stating post-marketing spontaneous reports "cannot be used to detect any differences in the safety profile of the different iron medicines".⁴

Therefore, the seventeen co-authors of this commentary wish to challenge the conclusions drawn in a recent *Prescrire* publication, which makes recommendations based on inferences that are inaccurate and clinically imprudent.⁵

In a recent criticism of the use of intravenous iron and a warning against one product, ostensibly less safe than others, the authors omitted all prospective and ininstitutional observational studies that have come to the opposite conclusion (see below).^{6,7} An example is found in the concluding paragraph: "Given the risk of serious hypersensitivity reactions as well as other adverse effects, the use of intravenous iron-containing products should be limited to situations in which the benefits clearly outweigh the harm. Iron sucrose is the best choice, as other products do not have a more favorable harm-benefit balance. The decision to keep iron dextran on the market is absurd: it protects the manufacturer while exposing patients to unnecessary risks". In contradistinction, an examination of published evidence suggests the above statements are simply incorrect. Below we highlight this evidence.

Shortly after recombinant erythropoietin was approved for correction of anemia in patients on dialysis, it became apparent that intravenous iron was necessary for an optimal erythropoietic response. High molecular weight iron dextran (HMWID, Imferon®), which is no longer available, was the only formulation used at first. While infrequent serious reactions were observed, safety concerns were raised. Then, in 1991, Imferon® was removed from market, but serendipitously at the same time, low molecular weight iron dextran (LMWID, INFED® in the United States and

CosmoFer® in Europe) was approved for use. The literature is rife with safety and efficacy reports, and serious adverse events with LMWID are extremely rare. It was not until 1996, when a HMWID (Dexferrum®), which is also no longer available, was released, that serious adverse events became frequent; numerous publications support this view.⁸ With HMWID now withdrawn from the market, there is no credible evidence supporting either increased efficacy or decreased safety with any of the remaining available formulations compared to any other. As a result, the US FDA wrote a letter to the American distributors of iron sucrose, which is now in the public domain, ordering them to remove all advertising claiming any safety advantage with iron sucrose.

Three prospective studies, a meta-analysis and an intra-institutional observational study at the Harvard Medical School hospitals^{6,7} report no significant efficacy or safety differences. A comparison of ferric carboxymaltose and LMWID in second and third trimester gravidas reported safety and efficacy without serious adverse events in either group.⁹ Supporting their conclusions in a single institution observational study using a prospective model for the integrated safety analysis, 1266 total dose infusions (1000 mg in 1 h) of low molecular weight iron dextran were given to 888 patients, 162 of whom were pregnant, intolerant of oral iron, or in whom oral iron was ineffective or contraindicated.¹⁰ No serious adverse events were observed. Low molecular weight iron dextran is the formulation currently being used for the first prospective study of intravenous iron in the second or third trimester of pregnancy in the US under an FDA IND (#114696). In a preliminary analysis of 57 of 60 planned subjects having completed study treatment to date, no serious adverse events have been observed. It should be noted that the total number of subjects included in these studies is small, and important adverse effects and relative differences in adverse events could be present that are not reflected in the studies.

In a prospective, controlled, randomized trial of 162 patients, comparing iron sucrose and ferumoxytol in patients with chronic kidney disease, the authors reported no difference in safety or efficacy.¹¹ The only prospective trial to report a significant safety difference between any of the formulations compared the now unavailable HMWID to ferric carboxymaltose and erroneously concluded, without differentiating the high and low molecular weight formulations, that ferric carboxymaltose had a safety advantage over iron dextran.¹² Corroborating data were recently published in a large meta-analysis of studies carried out in thousands of subjects who received intravenous iron.¹³

In an editorial accompanying the article, *Prescrire* reported that "there is no advantage to the use of iron dextran over iron sucrose and the risks of using iron dextran far outweigh the benefits". Not only is the statement without evidence to support it, but a replacement dose of intravenous iron sucrose requires four or five clinical visits compared to one visit with an infusion of 1000 mg of LMWID (a commonly used method approved in Europe but still off label in the US). The same advantage can be achieved with ferric carboxymaltose (approved as 1000 mg in 15 min in Europe and 750 mg in the US), iron isomaltoside (Europe only), and ferumoxytol (approval limited to 510 mg per visit).

Pre-medication with antihistamines is frequently administered without any data supporting their use. There are even published data suggesting that the majority of adverse events seen with intravenous iron, when intravenous diphenhydramine is used as pre-medication, are due to the pre-medication and mistakenly attributed to the intra-

venous iron.¹⁴ Antihistamines can cause flushing, hypotension, somnolence, and supraventricular tachycardia, prompting inappropriate intervention and the conversion of a minor reaction to a severe one. In contrast, there is a syndrome occurring in approximately 1:200 patients, consisting of arthralgias, myalgias or flushing, without associated hypotension, tachycardia, tachypnea, wheezing, stridor or periorbital edema. No intervention is necessary.¹⁵ After symptoms abate, re-challenge is appropriate. In the rare patient who reacts twice, the iron formulation should be changed. Antihistamines are inappropriate since measured tryptase levels after these reactions have always been normal.¹⁶ While post-marketing, spontaneous adverse event reporting can provide useful and important information, one simply cannot determine relative safety among formulations. Without head-to-head trials, such conclusions lack validity.

Parenteral iron is not just 'superior', it is a necessity since oral iron is ineffective in a number of clinical settings. Overstating the avoidance of intravenous iron is not only counterproductive but potentially harmful. Limiting its use will dramatically increase erythropoietin usage as well as transfusions and their associated complications. Essentially, all interpretable evidence supports the equivalent efficacy and safety of all of the current intravenous iron formulations. If minor infusion reactions occur with one formulation, switching to another is appropriate and safe.

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